IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Larry Caldwell, et al.	Art Unit: 1615
Serial No. 10/029,408	Examiner: Oh, Simon J.
Filed: December 26, 2001	Atty. Ref. CALD005
For: *Methods and Compositions for Treating Carpal Tunnel Syndrome*	

DECLARATION UNDER 37 C.F.R. 1.132

The Commissioner for Patents
Washington D.C. 20231

Dear Sir,

I, Larry Caldwell, am an inventor of the subject matter claimed in the patent application identified above. Enclosed is a copy of my C.V which demonstrates that I am qualified to speak on the level of one of skill in the art.

I hereby declare as follows:

1. I have read the Office Action dated January 26, 2004 for the above referenced application, as well as the references cited therein to support the rejections made by the Examiner.

2. US Patent No. 6,399,093 (the '093 patent) describes a method and composition to treat musculoskeletal compositions.

(a) The '093 patent does not teach or suggest the application of an NSAID formulation to an area about the carpal tunnel/lined an nerve.

(b) The only mention of carpal tunnel syndrome (CTS) in the '093 patent is a notation in the background section that describes that occupational injury may result in musculoskeletal injuries and notes CTS as an occupational hazard (abstract, col. 1, lines 27-43).

(c) The '093 patent does not specifically describe the treatment of carpal tunnel syndrome.

3. US Patent No. 5,980,921 (the '921 patent) describes topical compositions for regulating the oily/shiny appearance of skin.

(a) The '921 patent does not teach or suggest the application of an NSAID formulation to an area about the carpal tunnel/median nerve.

(b) The '921 patent does not describe the treatment of carpal tunnel syndrome.

4. US Patent No. 5,989,559 (the '599 patent) describes a banana peel extract composition and method of extraction. The '599 patent does not teach or suggest the application of an NSAID formulation to an area about the carpal tunnel/median nerve.

5. I am aware of no report of using a topical NSAID to treat carpal tunnel prior to the priority date of my application.

6. Prior to the work described in the subject application, one of skill in the art could not have had a reasonable expectation of success in a method of topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure. This lack of reasonable expectation of success in the claimed methods is based on the following premises:

(a) It is well known in the art that just because an active agent is administered orally to treat a medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition.

(b) It is well known in the art that just because an active agent is administered topically to treat one condition does not mean that it can be effective when topically administered to treat other conditions. This is particularly true if the sites of topical application differ.

(c) Because of the location of the target nerves which are responsible for carpal tunnel syndrome, it was not at all certain that the claimed methods would work prior to the actual reduction to practice reported in the application.

In the subject methods, the active agent must cross a barrier to reach the target site to be effective. Barriers are present in the area of the carpal tunnel/median nerve. The carpal tunnel is the interior of the wrist through which the medial nerve, tendons and blood vessels pass. Three sides of the carpal tunnel are bone and the other side is a thickened sheath, the flexor retinaculum, which is made of ligament material. Accordingly, for the subject methods to work, the target agent must cross this bone/ sheath barrier.

Furthermore, the active agent must penetrate deeply in order to reach a target site because carpal tunnel syndrome originates deep within the nerves of the wrist. Prior to my work in reducing the invention to practice, it was not at all certain that a sufficient amount of a given active agent would penetrate deeply enough to reach the target site.

Accordingly, in view of the above, based on the cited prior art teachings but without actual reduction to practice evidence, one of skill in the art would not have had a reasonable expectation of success in the claimed methods of topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure would be successful.

I hereby declare that all statements made herein of my own knowledge and are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued therefrom.

Respectfully submitted,

Date: 4/23/04

Larry Caldwell

LARRY J. CALDWELL

745-D Camden Avenue
Campbell, CA 95008

Tel: (408) 871-7331
Fax: (408) 374-0181

SUMMARY

Extensive experience in pharmaceutical research and development, with special emphasis on transdermal and gastro-intestinal dosage forms. Experience includes: dosage form design, pharmacology/toxicology, clinical protocol development, preparation and filing and management of INDs / NDAs with the US FDA.

EDUCATION

Ph.D., Pharmaceutical Science, **HOSHI UNIVERSITY** (Tokyo) Prof. Tsuneji Nagai **1985 - 1987**
M.A., Physiology, **UNIVERSITY OF KANSAS** **1973 - 1977**
B.S., Chemistry and Biology, **WASHBURN UNIVERSITY OF TOPEKA** **1968 - 1971**

PROFESSIONAL EXPERIENCE

TEIKOKU PHARMA USA, INC., Campbell, CA **2001 - present**
American subsidiary of Teikoku Seiyaku Co., Ltd., of Japan. One of the largest topical patch manufacturers in the world, with $200 million annual sales.

Vice President, Scientific Affairs
Manage all R&D, clinical development and regulatory affairs.

LARRY J. CALDWELL, Pharmaceutical Consultant (self-employed)

Product Development Consultant **1992 - 2001**
Provider of consulting services primarily for the development of dermal/transdermal dosage forms. Areas of expertise: formulation, pre-clinical pharmacology/toxicology, clinical study design, IND/NDA filing.

SOLA/BARNES-HIND, INC., Sunnyvale, CA **1988 - 1992**
Manufacturer of contact lenses, lens care products, and ophthalmic pharmaceuticals with $90 million annual sales.

Director, Lens Care R&D
Directed a staff of 28. Responsible for all aspects of contact lens care product development, including: formulation, microbiology, toxicology, analytical chemistry, packaging development, clinical supplies, process scale-up, and manufacturing validation of tablets and sterile solutions.

TEIKOKU SEIYAKU CO., LTD., Kagawa-ken, Japan **1985 - 1987**
Japanese pharmaceutical company more than 150 years old, specializing in ethical dermal and transdermal products with sales of $130 million annually.

Associate Director, R&D
Directed a staff of 15 researchers in the development of new transdermal and transmucosal drug delivery systems.

INTERx, MERCK AND COMPANY, INC., Lawrence, KS **1978 - 1985**
Wholly-owned subsidiary of Merck and Company specializing in research dedicated to controlled drug delivery systems.

Senior Research Fellow
Managed the Biology Department and directed outside studies to develop pharmacokinetic and pharmacodynamic profiles on new compounds and product prototypes.

UNIVERSITY OF KANSAS, Lawrence, KS **1977 - 1978**

Chemist, Department of Pharmaceutical Chemistry
Designed and conducted kinetic studies on new decontamination agents for chemical weapons.

HOECHST AG, Frankfurt/Main-Hoechst, Germany **1971 - 1973**

Bio-Ingeneur, Pharmacology Department - Gastroenterology
Performed a wide variety of in vitro and in vivo procedures involving small animal surgery and classical pharmacologic techniques.

PUBLICATIONS - Larry J. Caldwell

1. R. Schleyerbach, M. Classen, L.J. Caldwell and L. Demling. A long-acting secretin preparation: the effect on pancreatic secretion in dogs and on pentagastrin-induced peptic ulcers in cats. Acta Hepato-Gastroenterologica 20:428-434 (1973)

2. L. Caldwell, R. Cargill, W.R. Ebert and J.J. Windheuser. The ulcerogenic potential of orally administered dexamethasone in the rat: a comparison of a tablet formulation to soft-gelation-capsule formulations. Pharmaceutical Technology 3(7):52-56 (1979)

3. T. Nishihata, J.H. Rytting, T. Higuchi and L. Caldwell. Enhanced rectal absorption of insulin and heparin in rats in the presence of non-surfactant adjuvants. Journal of Pharmacy and Pharmacology 33:334-335 (1981)

4. N. Bodor, K.B. Sloan, R.J. Little, S.J. Selk and L. Caldwell. Soft drugs 4. 3-Spirothiazolidines of hydrocortisone and its derivatives. International Journal of Pharmaceutics 10:307-321 (1982)

5. T. Nishihata, J.H. Rytting, L. Caldwell, S. Yoshioka and T. Higuchi. Adjuvant effects on rectal absorption. *Optimization of Drug Delivery*, Alfred Benzon Symposium 17, Eds: H. Bundgaard, A.B. Hansen, H. Kofod. Munksgaard, Copenhagen, 1982

6. L. Caldwell, T. Nishihata, J.H. Rytting and T. Higuchi. Lymphatic uptake of water-soluble drugs after rectal administration. Journal of Pharmacy and Pharmacology 34:520-522 (1982)

7. S. Yoshioka, L. Caldwell and T. Higuchi. Enhanced rectal bioavailability of polypeptides using sodium 5-methoxysalicylate as an absorption promoter. Journal of Pharmaceutical Sciences 71(5):(1982)

8. J.J. Windheuser, J.L. Haslam, L. Caldwell and R.D. Shaffer. The use of N, N-diethyl-m-toluamide to enhance dermal and transdermal delivery of drugs. Journal of Pharmaceutical Sciences 71(11):1211-1213 (1982)

9. T. Nishihata, J.H. Rytting, A. Kamada, T. Higuchi, M. Routh and L. Caldwell. Enhancement of rectal absorption of insulin using salicylates in dogs. Journal of Pharmacy and Pharmacology 35:148-151 (1983)

10. M. Jay, R.M. Beihn, G.A. Snyder, J.S. McClanahan, G.A. Digenis, L. Caldwell and A. Mlodozeniec. In vitro and in vivo suppository studies with perturbed angular correlation and external scintigraphy. International Journal of Pharmaceutics 14:343-347 (1983)

11. P. Sithigorngul, P. Burton, T. Nishihata and L. Caldwell. Effects of sodium salicylate on epithelial cells of the rectal mucosa of the rat: a light and electron microscopic study. Life Sciences 33:1025-1032 (1983)

12. J.A. Fix, P.S. Leppert, P.A. Porter and L.J. Caldwell. Influence of ionic strength on rectal absorption of gentamicin sulfate in the presence and absence of sodium salicylate. Journal of Pharmaceutical Sciences 72:1134-1137 (1983)

13. L.J. Caldwell, T. Nishihata and T. Higuchi. Rectal absorption of parenteral drugs. Pharmaceutical Technology 7(10):50-55 (1983)

14. A.R. Mlodozeniec, L. Caldwell, M. Jay, R. Beihn and G.A. Digenis. Noninvasive monitoring of the in vivo release characteristics of rectal drug delivery devices. *Recent Advances in Drug Delivery Systems* Eds: James M. Anderson and Sung Wan Kim, 321-341. Plenum Publishing Corporation, 1984

15. T. Nishihata, J.H. Rytting, T. Higuchi, L.J. Caldwell and S.J. Selk. Enhancement of rectal absorption of water-soluble antibiotics in dogs. International Journal of Pharmaceutics **21**:239-248 (1984)

16. L. Caldwell, T. Nishihata, J. Fix, S. Selk, R. Cargill, C.R. Gardner and T. Higuchi. Absorption-promoting adjuvants: Animal studies on their effects on rectal drug absorption. Methods and Findings in Experimental and Clinical Pharmacology 6:503-507 (1984)

17. K.B. Sloan, S. Selk, J. Haslam, L. Caldwell and R. Shaffer. Acyloxyamines as prodrugs of anti-inflammatory carboxylic acids for improved delivery through skin. Journal of Pharmaceutical Sciences **73**(12): (1984)

18. L.J. Caldwell, A. Parr, R.M. Beihn, B.J. Agha, A.R. Mlodozeniec, M. Jay and G.A. Digenis. Drug distribution and biliary excretion pattern of a cyclic somatostatin analog: a comparison of ^{14}C labeled drug and a ^{131}I iodinated drug analog. Pharmaceutical Research 2:80-83 (1985)

19. M. Jay, R.M. Beihn, G.A. Digenis, F.H. Deland, L. Caldwell, and A.R. Mlodozeniec. Disposition of radiolabelled suppositories in humans. Journal of Pharmacy and Pharmacology **37**(4):266-268 (1985)

20. P. Mojaverian, R.K. Ferguson, P.H. Vlasses, M.L. Rocci Jr., A. Oren, J.A. Fix, L.J. Caldwell and C. Gardner. Estimation of gastric residence time of the Heidelberg capsule in humans: effect of varying food composition. Gastroenterology. **89**(2):392-397 (1985)

21. R. Cargill, K. Engle, G. Rork and L.J. Caldwell. Systemic delivery of timolol after dermal application: transdermal flux and skin irritation potential in the rat and dog. Pharmaceutical Research **3**:225-229 (1986)

22. T. Itoh, T. Higuchi and L.J. Caldwell. Dynamic friction of some film coatings on rat stomach mucosa in vitro - effect of pH. International Journal of Pharmaceutics **33**:265-267 (1986)

23. T. Itoh, T. Higuchi, C.R. Gardner and L. Caldwell. Effect of particle size and food on gastric residence time of non-distintegrating solids in beagle dogs Journal of Pharmacy and Pharmacology **38**:801-806 (1986)

24. T. Nishihata, P.R. Burton and L.J. Caldwell. Induction of microvillous fusion and pinching-off by concanavalin A. Biochem. Biophys. Res. Comm. **140**:766-772 (1986)

25. T. Nishihata, L.J. Caldwell and K. Sakai. Inhibitory effect of salicylate on 2,4-dinitrophenol and diethyl maleate in isolated rat intestinal epithelial cells. Biochim. Biophys. Acta **970**(1):7-18 (1988)

26. R. Cargill, L.J. Caldwell, K. Engle, J.A. Fix, P.A. Porter and C.R. Gardner. Controlled gastric emptying 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. Pharmaceutical Research 5(8):533-536 (1988)

27. K.L. Shih, M.K. Raad, J.C. Hu, W.J. Gresh, S.I. Jiries, L.J. Caldwell and M.V. Bergamini. Disinfecting activities of non-peroxide soft contact lens cold disinfection solutions. CLAO J. **17**(3):165-168 (1991)